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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,977	09/11/2003	Benjamin L. Viglianti	180/157/2/2	8988

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EXAMINER	
CHAO, ELMER M	
ART UNIT	**PAPER NUMBER**
3737	

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03/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,977	VIGLIANTI ET AL.	
	Examiner	Art Unit	
	ELMER CHAO	3737	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/27/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-34,36-40 and 42-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-34,36-40 and 42-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/9/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement of the amendment filed 2/27/2009 is made.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/27/2009 has been entered.

Response to Arguments

3. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

4. Regarding Applicants' arguments with respect to the newly added limitation "wherein the monitoring comprises monitoring release of the contents of the liposome at the desired site by monitoring an increase in the presence of the contrast agent released from the liposome at the desired site as the contents of the liposome are being released at the desired site", Examiner has changed the 102(b) rejection to cite a passage in Lang that corresponds to the limitation. Additionally, an alternative 103(a) rejection is made to show the obviousness of using real time drug monitoring.

5. Regarding Applicants' arguments with respect to the newly added limitation "wherein the liposome composition has the ability to remain in the subject's blood stream for a protracted period of time without being recognized by the subject's reticuloendothelial system", Examiner has provided a 103(a) rejection to show the obviousness of this limitation.

6. Regarding Applicants' arguments with respect to newly added claim 47, Examiner has provided a grounds of rejection for the claim.

7. Regarding Applicants' arguments with respect to the "real-time" feature taught by Unger et al. '935 (pages 29-30, Arguments), Examiner contends that Lang et al.'s disclosure of MR imaging temporally spaced apart does not necessarily preclude the step of real time imaging of the release of the contrast agent. Real time monitoring is a feature that is common and known in the field of medical imaging. Likewise, the benefits of real time imaging are also well-known in the field of medical imaging. The fact that Unger et al. '935 uses ultrasound rather than MRI to perform real time monitoring of the contrast agent does not prevent the combination of the two references. Similar to Lang et al., Unger et al. '935 also involves monitoring drug delivery. The benefit of using real time imaging in the field of monitoring drug delivery does not vary based on the modality being used. In this particular case, Unger et al. '935 teach that real time imaging can be used to visualize the accumulation of the therapeutic microspheres in order to trigger the release of the drug. The differences between the two references as argued by Applicants do not preclude the use of Unger

et al. '935 as a teaching reference. Therefore, the obviousness rejection utilizing Unger et al. '935 will be maintained.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. **Claim 42 and 43** is rejected under 35 U.S.C. 102(b) as being anticipated by Lang et al. (WO 98/44910). Lang et al. teach a method of monitoring the drug delivery to a tumor (page 5, lines 3-5), the method comprising:

(a) administering to a subject a non-sensitive liposome composition comprising:

(i) a contrast agent (page 5, lines 7-8), wherein the contrast agent comprises an element selected from the group consisting of Gd (page 3, lines 7 & 11);

(ii) a therapeutic agent (page 5, lines 14-15), wherein the therapeutic agent is a chemotherapeutic agent (page 7, lines 8-16); and

(iii) a non-sensitive liposome encapsulating the contrast agent and the compound of interest (page 5, lines 9-15); and

(b) monitoring the accumulation of the compound of interest at the tumor site by magnetic resonance imaging (page 5, lines 16; page 5, lines 3-5; By monitoring via MRI imaging, the operator would be able to visually examine

differences in pixel densities.), wherein the monitoring comprises monitoring release of the contents of the liposome at the desired site by monitoring an increase in the presence of the contrast agent released from the liposome at the desired site as the contents of the liposome are being released at the desired site (page 16, lines 13-15).

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. **Claims 19, 20, 26-28, and 47** are rejected and **claim 42 and 43 are alternatively** rejected under 35 U.S.C. 102(b) as being anticipated by Lang et al. in view of Unger et al. (U.S. 5,542,935), henceforth referred to as Unger '935.

Regarding **claims 42 and 43,** Lang et al. teach all the limitations as described above but may fail to teach the monitoring of the compound being performed in real time. However, in the same field of endeavor, Unger '935 teach the monitoring of the drug delivery and accumulation in real time (col. 36, lines 6-25). Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the invention to monitor the liposome delivery in real time as it is considered an obvious solution to the common problem of monitoring drug delivery (for motivation see col. 36, lines 6-25). Additionally, real time imaging is used to visualize the accumulation of the therapeutic

microspheres in order to trigger the release of the drug (for motivation see col. 36, lines 6-25).

Regarding **claims 19, 20, and 26-28,** Lang et al. teach the limitations as discussed above but fail to explicitly teach the composition having the ability to remain in the subject's blood for a protracted period of time without being recognized by the reticuloendothelial system. However, in the same field of endeavor, Unger '935 teach using coated microspheres to avoid detection by the reticuloendothelial system (col. 19, lines 42-44). Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the invention to use a liposome composition that has the ability to remain the subject's blood for a protracted period of time without being recognized by the reticuloendothelial system in order to withstand recirculation and to avoid uptake by the reticuloendothelial system (for motivation see col. 19, lines 40-44).

Regarding **claim 47**, Lang et al. teach the limitations as discussed above. Lang et al. does not explicitly teach that the blood pool is indicative of a vascular irregularity. However, in one of Lang et al.'s disclosed examples, Lang et al. teach the liposomal contrast agent being used to probe capillary permeability and pore size in vivo (page 15, lines 15-23). Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the invention to include having the blood pool be indicative of a vascular irregularity in order to determine the optimal particle size of liposomes carrying the therapeutic agents for treatment of a particular type of disease (for motivation see page 15, lines 18-20).

12. **Claims 8, 12, 13, 15-18, 22-25, 29-31, 33, 34, 44, and 46** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. in view of Unger '935, and further in view of Fenn et al. (U.S. 5,810,888). Lang et al. teach all of the limitations as discussed above. Lang et al. do not explicitly teach the use of a thermo-sensitive liposome for drug delivery. Fenn et al. teach the use of a thermo-sensitive liposome for drug delivery by transmitting electromagnetic radiation to the site of interest wherein the liposome contains chemotherapy agents (col. 17 & claims 15-17, the thermal breakdown of thermo-sensitive liposomes would release the contrast agent disclosed by Lang et al.). Fenn et al. also teach the possibility of using medical imaging modalities such as Magnetic Resonance Imaging to detected the temperature of the site while heating (col. 9, lines 21-27). It would have been obvious to a person of ordinary skill in the art to modify Lang et al. to include the use of a thermo-sensitive liposome in the method of drug delivery and monitoring as evidenced by Fenn et al. Such a modification would increase the concentration of a drug within the tumor during drug delivery (col. 2, lines 19-22).

13. **Claims 9-11, 14, 24, 32, 36-40, and 45** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. in view of Unger '935, further in view of Fenn et al., and further in view of Unger (U.S. 5,149,319), henceforth referred to as Unger '319.

Regarding **claims 9-11, and 37-40**, Lang et al., Unger '935, and Fenn et al. teach the limitations as discussed above. Lang et al. do not explicitly teach the use of ultrasound to heat the tumor site. However, Unger '319 teaches the use of ultrasound

to heat the tumor site (col. 1, lines 54-58). Therefore, it would have been obvious to a person of ordinary skill in the art at the time of the invention to modify Lang et al. to include the use of ultrasound to heat the tumor site as evidenced by Unger '319. Such a modification would be advantageous by causing tumor cells to die, eventually destroying the tumor (col. 1, lines 24-31, by heating the site of interest, blood flow is also increased).

Regarding **claims 14, 24, 32, and 36,** all the limitations are disclosed as discussed above. None of the references described except for Unger '935 discloses a particular formulation of a thermo-sensitive liposome. Unger '935 discloses many different formulations of liposomes, including DPPC-PEG (col. 19, lines 24-39). Therefore, it would have been obvious to a person of ordinary skill in the art to use a thermo-sensitive liposome comprising a formulation of PEG and DPPC. Liposomes are often liked to polymers of polyethylene glycol in order to achieve greater stability (col. 19, lines 24-27). Dipalmitoylphosphatidylcholine is used in thermo-sensitive liposomes for their ability to rupture on application and for their stability (col. 19, lines 36-39).

Regarding **claim 45**, by monitoring the release of the of the contrast agent, a temperature will be inherently reached by the thermosensitive liposome which would serve to release the contrast agent.

14. **Claim 21** is rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. in view of Unger '935, and further in view of Gamble et al. (U.S. 4,728,575). Lang '910 discloses all of the limitations as discussed above. Lang '910 does not describe a

liposome wherein the liposome comprises DSPC/Cholesterol. However, Gamble '575 teaches the use of a liposome comprising DSPC/Cholesterol (C4, L14). It would have been obvious to a person of ordinary skill in the art at the time of the invention to modify Lang '910 to use a lipid formulation of DSPC/Cholesterol as evidenced by Gamble '575. Such a modification would be advantageous in MRI contrast agent enhancement by promoting vesicle stability of the liposome that encapsulates the contrast agent (abstract).

Conclusion

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ELMER CHAO whose telephone number is (571)272-0674. The examiner can normally be reached on 9am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Casler can be reached on (571)272-4956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BRIAN CASLER/
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3/17/2009